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Editorial

Settling the "score" with liver cancer ☆

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Chronic hepatitis B viral (HBV) infection remains a serious public health problem worldwide, as more than two billion people have been infected and 350 million are chronically infected [1,2]. Chronicity rates vary based on routes of exposure, with a chronicity rate of 5% in adult acquisition versus 90% in newborns [3]. 15–40% of chronically infected patients will develop adverse sequelae including cirrhosis, hepatic decompensation, and hepatocellular carcinoma [4–6].

Hepatocellular carcinoma (HCC), a potentially serious late complication of HBV infection, is now the fifth most common malignancy worldwide, especially in Asia and Africa [7,8]. The risk of developing HCC in patients with cirrhosis due to chronic HBV is about 1.5% per year [8,9]. Although HCC is more common in the setting of cirrhosis, with data showing that approximately 75% of HCC cases occur in patients with cirrhosis, cirrhosis may not necessarily precede HCC in HBV-infected people [10]. Zaman et al. in their study of 448 patients with HBV-associated HCC identified that in 70% of cases, HCC was diagnosed before cirrhosis was recognized [8,10]. As the prognosis of patients with late stage HCC is often grim, earlier detection of small tumors offers the potential for curative therapy. Hence, screening of high-risk populations has been recommended and various strategies have been advocated in an effort to identify and effectively treat early HCC and improve overall mortality.

In addition to proper screening, identification of risk factors for the development of HCC plays an important role in prevention. As the global burden of HBV infection is enormous, it is virtually impossible to screen all infected patients for HCC. Therefore, the identification of risk factors, target populations, and predictive models are needed to help focus screening to the infected population that is most at risk for the development of HCC. In this issue of the *Journal of Hepatology*, Yuen et al. [11] attempt not only to identify the risk factors for HCC in patients with HBV, but also to develop a predictive risk score for patients at high risk for development of HCC.

In this longitudinal study over a period of 10 years, 820 treatment naïve patients with chronic HBV were followed at a liver clinic at Queen Mary's Hospital in Hong Kong. These patients were followed every 3–6 months, and were monitored with HBV serology, liver biochemistry, and alpha-fetoprotein. Patents underwent radiologic imaging only if AFP levels were greater than 20 ng/mL. The primary endpoint was a diagnosis of HCC by either a positive histology or elevated AFP levels with imaging compatible with HCC.

Of the 820 patients followed, 40 (4.9%) developed hepatocellular carcinoma. After analysis of the collected data, Yuen et al. [11] identified various virological and host risk factors for the development of HCC. In univariate analysis, male gender, older age, higher HBV DNA levels, presence of core promoter mutations, ALT >0.5 X ULN, and pre-existing cirrhosis were significant risk factors for the development of HCC. Of the other indices, such as comparing genotype B and C, precore and wild-type mutations, HBeAg/anti-HBe status on presentation, and HBeAg/anti-HBe seroconversion, no difference in the risk of HCC was found. Combining these data in a multivariable Cox Regression model, male gen-

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der (HR 2.98), increasing age (HR 1.07), higher HBV DNA levels (HR 1.28), core promoter mutations (HR 3.66), and presence of cirrhosis (HR 7.31) were independently associated with the development of HCC.

With these independent associations, Yuen et al. [11] then created a predictive scoring system for the development of HCC by using a logistic regression equation including gender, age, HBV DNA, cirrhosis, and core promoter mutation. This scoring system, the "Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis" (GAGHCC), attempts to predict the 5- and 10-year risk of development of HCC. The optimal cut-off of the HCC score for the prediction of 5- and 10-year development of HCC is 101, and once this threshold is reached, the risk increases exponentially. As core promoter mutations are not typically analyzed in clinical practice, Yuen et al. [11] then reformulated, tested, and had similar results in this predictive scoring system without the use of core promoter mutations.

As HBV and HCC are major global problems, early identification of high-risk populations with the utilization of a validated scoring system allows for significant streamlining of screening modalities. However in this study, there were only 40 cases of HCC. Thus Yuen et al. [11] may have oversaturated their regression model with the analysis of six variables. Additionally, the authors validated the GAGHCC predictive score by performing the leave-one-out cross validation analysis. This method, although mathematically sound, is still not as effective as validation in another cohort of patients. Hence, further validation needs to be performed on other populations, including both high-risk and low-risk patients.

It is reassuring that the risk factors identified by Yuen et al. [11] have been shown in other studies to be associated with HCC. Interestingly, HBeAg status and HBV genotype were not found to be significantly associated with HCC in their model. In contrast to these results, Yang et al. in a prospective population-based study following 11,893 men for the development of hepatocellular carcinoma reached different conclusions [12]. They identified that the incident rate of HCC was approximately 3-fold higher in individuals who were positive for both HBsAg and HBeAg, as compared to men who were positive for HBsAg and negative for HBeAg [12].

Yuen et al. [11] also found no difference in the cumulative risk of HCC when comparing patients with genotype B or C. Previous studies suggested a difference in HCC risk based on genotypes. In a prospective cohort study of 1006 patients in Hong Kong, where 86 developed HCC, genotype C was independently associated with a higher risk of HCC than genotype B (HR:3.83; 95% CI, 2.15 to 6.81; $P < .0001$) [13]. In the current paper, Yuen et al. [11] made the argument that as basal core promoter (BCP) mutations are more common in genotype C, it is the BCP mutation that is the actual risk factor for HCC rather than genotype. However, in another study controlling for BCP status, Yang et al. showed that genotype C was an independent risk factor for HCC [14]. As genotyping and mutation analysis become more available, this issue will need to be clarified.

Yuen et al. [11] derived this scoring system from a cohort of Chinese patients in a hospital liver clinic, which could contribute to a selection bias. As the incidence of HCC differs by race [3,15], it is unclear if this scoring system will be applicable to the non-Asian population. Clearly, future validation studies are needed in patients from different regions and other ethnicities. With validation, this "GAGHCC" scoring system may become a helpful screening tool.

In the past two decades, we have made great strides in addressing chronic HBV infection as a global health problem. The success of HBV vaccination in various parts of the world has reduced the prevalence of infection, and ultimately, hepatocellular carcinoma [16]. However, much work is still needed in this field, as there is a huge demand for HCC surveillance. The ability for risk stratification of patients with HBV in predicting HCC not only addresses important public health issues, but also provides a rationale for resource allocation in health care. Yuen et al. [11] have attempted to consolidate the work of many in an effort to "push the envelope" even further. After identification of various independent risk factors for the development of HCC in the setting of chronic HBV, they introduce a novel predictive scoring system for the development of HCC. This scoring system combines each of the individual risk factors together to obtain an estimate of the overall risk for an individual patient.

The future of the fight against chronic HBV and HCC appears to be a bright one, as the field of medicine continues to evolve. The move towards genomic medicine with the application of genome wide association studies will hopefully identify genetic factors that predispose HBV patients to the development HCC. The combination of genetic information in conjunction with a validated predictive scoring system based on various clinical parameters may promise a more personalized approach to medicine, ultimately leading to improved patient care.

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